

CLAIMS

1. A composition adapted for injection into the blood-stream and body cavities of living beings, e.g. for the purpose of ultrasonic echography, consisting of a suspension of air or gas microbubbles in a physiologically acceptable aqueous carrier phase comprising from about 0.01 to about 20% by weight of one or more dissolved or dispersed surfactants, characterized in that at least one of the surfactants is a film forming surfactant present in the composition at least partially in lamellar or laminar form.

2. The composition of claim 1, characterized in that the lamellar surfactant is in the form of mono- or pluri-molecular membrane layers.

3. The composition of claim 1, characterized in that the lamellar surfactant is in the form of liposome vesicles.

4. The composition of claim 1, characterized in that it essentially consists of a liposome solution containing air or gas microbubbles developed therein.

5. The composition of claim 4, characterized in that the size of most of both liposomes and microbubbles is below 50 μm , preferably below 10 μm .

6. The composition of claim 1, containing about $10^8 - 10^9$ bubbles of 0.5 - 10 μm size/ml, said concentration showing little or substantially no variability under storage for at least a month.

7. The composition of claim 1, characterized in that the surfactants are selected from phospholipids including the lecithins such as phosphatidic acid, phosphatidyl-choline, phosphatidyl-ethanolamine, phosphatidyl-serine, phosphatidyl-glycerol phosphatidyl-inositol, cardiolipin and sphingomyelin.

8. The composition of claim 7, characterized in further containing substances affecting the properties of liposomes selected from phosphatidyl-glycerol, dicetyl-phosphate, cholesterol, ergosterol, phytosterol, sitosterol, lanosterol, tocopherol, propyl gallate, ascorbyl palmitate and butylated hydroxy-toluene.

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9. The composition of claim 1, further containing dissolved viscosity enhancers or stabilizers selected from linear and cross-linked poly- and oligo-saccharides, sugars, hydrophilic polymers and iodinated compounds such as Iopamidol in a weight ratio to the surfactants comprised between about 1:5 to 100:1.

10. The composition of claim 1, in which the surfactants comprise up to 50% by weight of non-lamellar surfactants selected from fatty acids, esters and ethers of fatty acids and alcohols with polyols such as polyalkylene glycols, polyalkylenated sugars and other carbohydrates, and polyalkylenated glycerol.

11. A method for the preparation of the suspensions of claim 1, characterized by the following steps:

(a) selecting at least one film forming surfactant and converting it into lamellar form;

(b) contacting the surfactant in lamellar form with air or an adsorbable or entrappable gas for a time sufficient for that air or gas to become bound by said surfactant; and

(c) admixing the surfactant in lamellar form with an aqueous liquid carrier, whereby a stable dispersion of air or gas microbubbles in said liquid carrier will result.

12. The method of claim 11, in which step (c) is brought about before step (b), the latter being effected by introducing pressurized air or gas into the liquid carrier and thereafter releasing the pressure.

13. The method of claim 11, in which step (c) is brought about by gentle mixing of the components, no shaking being necessary, whereby the air or gas bound to the lamellar surfactant in step (b) will develop into a suspension of stable microbubbles.

14. The method of claims 11 or 12, in which the liquid carrier contains dissolved therein stabilizer compounds selected from hydrosoluble proteins, polypeptides, sugars, poly- and oligo-saccharides and hydrophilic polymers.

15. The method of claim 11, in which the conversion of step (a) is effected by coating the surfactant onto particles of soluble or insoluble materials; step (b) is effected by letting the coated particles stand for a while under air or a gas; and

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step (c) is effected by admixing the coated particles with an aqueous liquid carrier.

16. The method of claim 11, in which the conversion of step (a) is effected by sonicating or homogenizing under high pressure an aqueous solution of film forming lipids, this operation leading, at least partly, to the formation of liposomes.

17. The method of claim 16, in which step (b) is effected by freeze-drying the liposome containing solution, the latter optionally containing hydrophilic stabilizers and contacting the resulting freeze-dried product with air or a gas for a period of time.

18. The method of claims 16 and 17, in which the water solution of film forming lipids also contains viscosity enhancers or stabilizers selected from hydrophilic polymers and carbohydrates in weight ratio relative to the lipids comprised between 1:5 and 100:1.

19. A dry pulverulent formulation which, upon dissolution in water, will form an aqueous suspension of microbubbles for ultrasonic echography, characterized in containing one or more film forming surfactants in laminar form and hydrosoluble stabilizers.

20. The dry formulation of claim 19, in which the surfactants in laminar form are in the form of fine layers deposited on the surface of soluble or insoluble solid particulate material.

21. The dry formulation of claim 20, in which the insoluble solid particles are glass or polymer beads.

22. The dry formulation of claim 20, in which the soluble particles are made of hydrosoluble carbohydrates, polysaccharides, synthetic polymers, albumin, gelatin or Iopamidol.

23. The dry formulation of claim 19, which comprises freeze-dried liposomes.

24. The use of the injectable composition of claim 1 for ultrasonic echography.

25. The use of the injectable composition of claims 1-10 for transporting in the blood-stream or body cavities bubbles of

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foreign gases active therapeutically or diagnostically.

26. The composition of claim 4, in which the surfactant comprises, bound thereto, bioactive species designed for specific targeting purposes, e.g. for immobilizing the bubbles in specifically defined sites in the circulatory system, or in organs, or in tissues.

27. The composition of claim 4, in which the surfactant comprises, bound thereto, bioactive species selected from monoclonal antibodies, antibody fragments or polypeptides designed to mimic antibodies, bioadhesive polymers, lectins and other receptor recognizing molecules.

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